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Communication

Design, synthesis, and fungicidal activity of novel 1,3,4-oxadiazole derivatives

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ABSTRACT

Employing the intermediate derivatization method (IDM), twenty novel 1,3,4-oxadiazole derivatives containing arylpyrazoloxyl moiety were designed and synthesized. The structures of the title compounds were identified by ¹H NMR, ¹³C NMR, MS and elemental analyses, compound **4** was further identified by single-crystal X-ray diffraction. Antifungal activities against rice sheath blight (RSB) and sorghum anthracnose (SA) were evaluated by the mycelium linear growth rate method. Compounds **4**, **16** and **20** displayed significant activities against RSB (EC₅₀ = 0.88 mg/L, 0.91 mg/L and 0.85 mg/L, respectively), higher than the reference tebuconazole; While compound **3** exhibited higher activity against SA (EC₅₀ = 1.03 mg/L), equal to commercial pyraclostrobin (EC₅₀ = 1.06 mg/L). The study showed that compound **20** is a promising fungicide for further development.

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Rice sheath blight (*Rhizoctonia solani* Kühn, RSB) is one of the three important diseases (rice sheath blight, bacterial blight and rice blast) of rice. Meanwhile, sorghum anthracnose (*Colletotrichum graminicola* (Cesati) Wilson, SA) is also a worldwide disease, which occurs at all stages of sorghum growth. It was reported that both RSB and SA can cause 10%–30% even 40%–50% production loss in crops per year worldwide [1,2]. The use of fungicides can effectively reduce crop loss and further to guarantee crop harvest. At present, the existing pesticides for control of RSB are mainly tebuconazole, pyraclostrobin and azoxystrobin; and thiram and prochloraz for control of SA. However, the fungus will develop resistance subsequently after these agrochemicals are used for a while. The Fungicide Resistance Action Committee (FRAC) reported that the fungicides with known modes of action are classified according to target sites into more than 50 groups [3]. Unfortunately over 80% target sites have already developed medium to high resistance risk to many familiar classes of fungicides, which involved the vast majority of fungicide structures. So it is an urgent demand for developing continually novel and highly active fungicides with different modes of action to address the increasingly serious resistance problem.

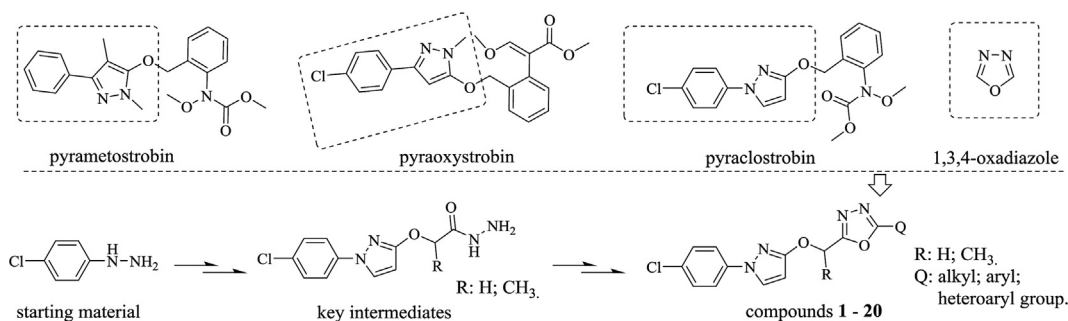
1,3,4-Oxadiazole derivatives have been paid more and more attention since Gibson reported cyclization mechanism of this type of compounds in 1962 firstly [4]. The derivatives of 1,3,4-oxadiazoles often exhibit broad biological activities in medicine [5–9] and agriculture. For agrochemicals, Song *et al.* [10], introduced phenoxymethyl moiety into 1,3,4-oxadiazole to afford insecticides; Zhang *et al.* [11], discovered antimicrobial agents by importing phenylpyrazolyl to 1,3,4-oxadiazole. Zhang *et al.* [12], inserted piperazine to 1,3,4-oxadiazole and obtained compounds which exhibited broad spectrum herbicidal and fungicidal activities. Some literatures also disclosed 1,3,4-oxadiazoles containing phenyl [13], pyridyl [14], thiazole ring [14] as agrochemicals. On the other side, the arylpyrazole derivatives have been playing an important role both in medicinal [15,16] and crop protection fields [17], too. The main varieties containing arylpyrazole substructure include pyrametostrobin [18,19], pyraoxystrobin [20] and pyraclostrobin [21,22]. Although these three fungicides all belong to strobilurin, they focus on different targets, rice sheath blight and rice blast, downy mildew, and powdery mildew, respectively. Scholars have been carrying out studies on taking arylpyrazole as structural units of pesticides. Wang *et al.* [23], found pyridylpyrazole acid derivatives can be used as lead compounds for further development of novel insecticides. Wu *et al.* [24], demonstrated that arylpyrazole carboxamide derivatives exhibited broad-spectrum insecticidal activities. Wang *et al.* [25], achieved heterocyclic compounds containing pyridylpyrazole not only displayed

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Scheme 1. An overview of the design of 1,3,4-oxadiazole derivatives.

excellent fungicidal activities, but also exhibited modest insecticidal activities. Therefore, arylpyrazole is a magical and formidable chemical group, which is worthy of being applied further.

In this study, to develop new fungicides with high biological activity, based on the excellent performance of the above two kinds of compounds, under the direction of the intermediate derivatization methods (IDM) [26–32], we introduced arylpyrazoloxyl to 1,3,4-oxadiazole and designed a series of novel 1,3,4-oxadiazole derivatives using 4-chlorophenylhydrazine as the starting material (Scheme 1). The detailed synthesis, bioassays and structure-activity relationship of these derivatives were discussed below.

All chemicals such as starting materials and reagents were commercially available (Sinopharm Chemical Reagent Co., Ltd., China) and used without further purification. Melting points were determined on a Büchi M-569 melting point apparatus and were uncorrected. ¹H NMR and ¹³C NMR spectra were recorded with a Mercury 300 MHz spectrometer with deuteriochloroform (CDCl₃) or DMSO-*d*₆ as the solvent and tetramethylsilane (TMS) as the internal standard. Elemental analyses were determined on an elemental Vario EL cube instrument. The mass spectra were acquired with an Agilent 1100 series LC/MSD Trap equipped with electron spray ionization (ESI) source. X-ray structure determination was recorded with Bruker D8 Quest Single crystal X-ray diffractometer. The isolation of the compounds was conducted by Biotage Isolera Prime flash purification system.

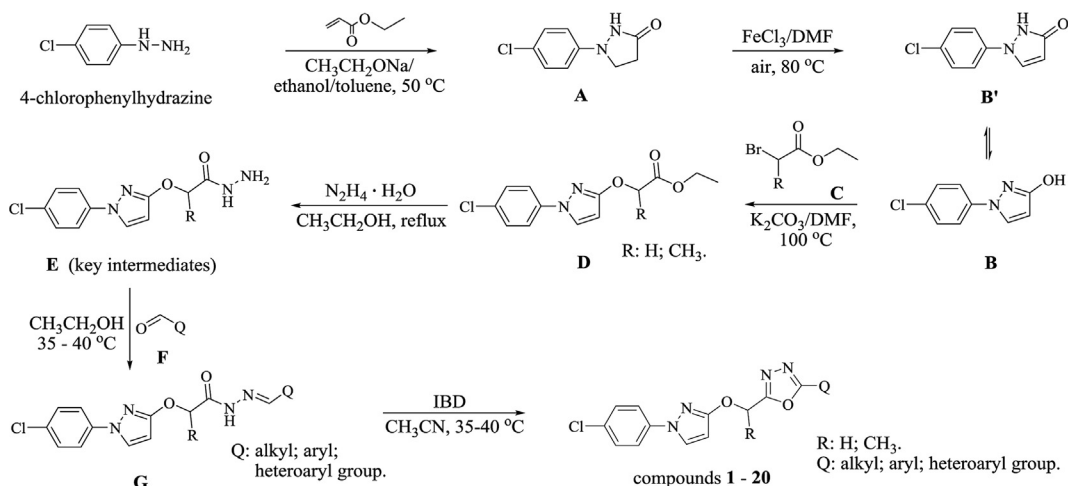
The general synthetic methods for compounds 1–20 are shown in Scheme 2. Intermediates A and B/B' were prepared according to the previously reported methods [33]. The general procedures for synthesis of intermediates D, E, G and compounds 1–20 were listed in Supporting information.

The crystal structure of target compound 4 was also determined by X-ray diffraction analyses (The atomic coordinates for compound 4 have been deposited at the Cambridge Crystallographic Data Centre. CCDC ID: 1572037 contain the supplementary crystallographic data for this article. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif). Its crystal structure is shown in Fig. 1.

The antifungal activities *in vitro* of all the synthesized compounds against two plant pathogenic fungi (RSB and SA) were conducted by the mycelium linear growth rate method as previously reported [34]. The final concentration of the test compound in the culture medium was 100, 50, 25, 12.5, 6.25 and 3.125 mg/L. For details, see Supporting information. The test results of the fungicidal activities of compounds 1 to 20 against RSB and SA are listed in Table 1.

According to the scheme described in Scheme 2, twenty title compounds were designed and synthesized, their chemical structures were summarized in Table 1. The synthesized compounds were characterized by ¹H NMR, ¹³C NMR, MS and elemental analyses. The chemical structure of compound 4 was also unequivocally determined by X-ray crystallography (Fig. 1).

In vitro bioassays indicated that these compounds have moderate to significant fungicidal activity against RSB and SA. Especially, compounds 4, 16 and 20 displayed excellent activities against RSB (EC₅₀ = 0.88, 0.91 and 0.85 mg/L, respectively), higher than the reference tebuconazole; While compound 3 exhibited higher activity against SA (EC₅₀ = 1.03 mg/L), equal to commercial pyraclostrobin (EC₅₀ = 1.02 mg/L). In general, the fungicidal activity of the tested compounds against RSB is superior to that against SA,



Scheme 2. Synthetic route of compounds 1–20.

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